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Kathryn B. Holroyd

Lisa Fosdick

Gwenn S. Smith

Jeannie Marie Leoutsakos

Cynthia A. Munro

See next page for additional authors

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Authors

Kathryn B. Holroyd, Lisa Fosdick, Gwenn S. Smith, Jeannie Marie Leoutsakos, Cynthia A. Munro, Esther S. Oh, Kristen E. Drake, Paul B. Rosenberg, William S. Anderson, Stephen Salloway, J. Cara Pendergrass, Anna D. Burke, David A. Wolk, David F. Tang-Wai, Francisco A. Ponce, Wael F. Asaad, Marwan N. Sabbagh, Michael S. Okun, Gordon Baltuch, and et al.

Deep brain stimulation targeting the fornix for mild Alzheimer dementia: design of the ADvance randomized controlled trial

Kathryn B Holroyd¹
 Lisa Fosdick²
 Gwenn S Smith¹
 Jeannie-Marie Leoutsakos¹
 Cynthia A Munro¹
 Esther S Oh¹
 Kristen E Drake²
 Paul B Rosenberg¹
 William S Anderson¹
 Stephen Salloway³⁻⁵
 J Cara Pendergrass⁶
 Anna D Burke⁷
 David A Volk⁸
 David F Tang-Wai⁹⁻¹¹
 Francisco A Ponce¹²
 Wael F Asaad^{13,14}
 Marwan N Sabbagh¹⁵
 Michael S Okun¹⁶
 Gordon Baltuch¹⁷
 Kelly D Foote¹⁸
 Steven D Targum^{2,6}
 Andres M Lozano^{10,11}
 Constantine G Lyketsos¹

¹Johns Hopkins University Memory and Alzheimer's Treatment Center, Baltimore, MD; ²Functional Neuromodulation Ltd, Minneapolis, MN; ³Department of Neurology, Butler Hospital; ⁴Department of Neurology, Rhode Island Hospital; ⁵Department of Neurology, Warren Alpert Medical School of Brown University, Providence, RI; ⁶Clintara LLC, Boston, MA; ⁷Banner Alzheimer's Institute, Phoenix, AZ; ⁸Penn Memory Center, Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA; ⁹Department of Neurology, ¹⁰Department of Neurosurgery, University of Toronto, ¹¹Division of Neurology, University Health Network Memory Clinic, Toronto, ON, Canada; ¹²Division of Neurological Surgery, Barrow Neurological Institute, St Joseph's Hospital and Medical Center, Phoenix, AZ; ¹³Department of Neurosurgery, Rhode Island Hospital; ¹⁴Department of Neurosurgery, Warren Alpert Medical School of Brown University, Providence, RI; ¹⁵Banner Sun Health Research Institute, Sun City, AZ; ¹⁶Center for Movement Disorders and Neurorestoration, Department of Neurology, University of Florida – Gainesville, Gainesville, FL; ¹⁷Center for Functional and Restorative Neurosurgery, University of Pennsylvania, Philadelphia, PA; ¹⁸Department of Neurosurgery, Center for Movement Disorders and Neurorestoration, University of Florida, Gainesville, FL, USA

Correspondence: Constantine G Lyketsos
 Chair's Office, Department of Psychiatry, Johns Hopkins Bayview, 5300 Alpha Commons Drive, Baltimore, MD 21224, USA
 Tel +1 410 550 0062
 Fax +1 410 550 1407
 Email kostas@jhmi.edu

Background: There are currently few available treatments and no cure for Alzheimer disease (AD), a growing public health burden. Animal models and an open-label human trial have indicated that deep brain stimulation (DBS) of memory circuits may improve symptoms and possibly slow disease progression. The ADvance trial was designed to examine DBS of the fornix as a treatment for mild AD.

Methods: ADvance is a randomized, double-blind, placebo-controlled, delayed-start, multi-center clinical trial conducted at six sites in the US and one site in Canada. Eighty-five subjects initially consented to be screened for the trial. Of these, 42 subjects who met inclusion and exclusion criteria were implanted with DBS leads anterior to the columns of the fornix bilaterally. They were randomized 1:1 to DBS “off” or DBS “on” groups for the initial 12 months of follow-up. After 1 year, all subjects will have their devices turned “on” for the remainder of the study. Postimplantation, subjects will return for 13 follow-up visits over 48 months for cognitive and psychiatric assessments, brain imaging (up to 12 months), and safety monitoring. The primary outcome measures include Alzheimer's Disease Assessment Scale – cognitive component (ADAS-cog-13), Clinical Dementia Rating sum of boxes (CDR-SB), and cerebral glucose metabolism measured with positron emission tomography. This report details the study methods, baseline subject characteristics of screened and implanted participants, and screen-to-baseline test–retest reliability of the cognitive outcomes.

Results: Implanted subjects had a mean age of 68.2 years, were mostly male (55%), and had baseline mean ADAS-cog-13 and CDR-SB scores of 28.9 (SD, 5.2) and 3.9 (SD, 1.6), respectively. There were no significant differences between screened and implanted or nonimplanted subjects on most demographic or clinical assessments. Implanted subjects had significantly lower (better) ADAS-cog-11 (17.5 vs 21.1) scores, but did not differ on CDR-SB. Scores on the major outcome measures for the trial were consistent at screening and baseline.

Conclusion: ADvance was successful in enrolling a substantial group of patients for this novel application of DBS, and the study design is strengthened by rigorous subject selection from seven sites, a double-blind placebo-controlled design, and extensive open-label follow-up.

Keywords: deep brain stimulation, Alzheimer disease, fornix, methods, clinical trials

Introduction

Alzheimer disease (AD) is the most common neurodegenerative dementia, affecting an estimated 5.4 million people¹ and costing as much as \$214 billion annually in the US alone.² New cases of AD continue to increase at an alarming rate worldwide, and its economic and health burden are projected to expand substantially in the next 50 years.³ Currently, there is no cure for AD. US Food and Drug Administration (FDA)-approved medications, including three cholinesterase inhibitors and one noncompetitive

N-methyl-D-aspartic acid receptor antagonist, temporarily ameliorate some symptoms in a subset of patients.¹ Phase II and III trials of putative disease-modifying therapies targeting the amyloid protein aggregations observed in AD have largely been unsuccessful in preventing disease progression.⁴⁻⁷ Additionally, the long-term safety of these treatments remains to be determined. Clearly, there is a great need for more specific and efficacious therapies for AD.

Converging evidence from neuropathological and in vivo imaging studies has demonstrated the vulnerability of the hippocampus and heteromodal association cortices in AD, as well as decreased functional connectivity in cortico-cortical and cortico-hippocampal circuits.^{8,9} Approaching AD as a dysfunction in cortico-cortical and cortico-hippocampal circuits suggests that modulating neuronal activity within these networks may be a viable treatment option for early AD. Deep brain stimulation (DBS) is a neurosurgical technique that has shown success modulating pain,¹⁰ motor dysfunction,^{11,12} and mood^{13,14} circuits in conditions for which pharmacologic treatments are not effective. The importance of developing circuitry-based therapeutic approaches to modulate cortical and hippocampal networks affected in AD was the impetus for a Phase I study of DBS of the fornix in early AD patients.¹⁵

The fornix is a white matter bundle that connects the hippocampus with other components of the limbic system,^{16,17} forming circuits that have been implicated in episodic memory.^{18,19} Recent diffusion tensor imaging (DTI) studies have shown white matter reductions in the fornix of individuals with AD.²⁰ In fact, fornix atrophy may precede both hippocampal degeneration and clinical symptoms of AD and predict conversion from mild cognitive impairment (MCI) to AD.^{21,22} This growing body of evidence, combined with rodent studies showing that DBS of the Papez circuit improves memory and promotes neurogenesis,^{23,24} indicates that DBS targeting of the fornix region (DBS-f) may be an effective treatment for AD symptoms. In the open-label Phase I trial of six AD subjects treated with DBS-f for 12 months, positron emission tomography (PET) scans showed an increase in cortical glucose metabolism and increased cortical functional connectivity over 1 year¹⁵ in contrast to the decreases in cortical metabolism and functional connectivity typically observed in AD.²⁵⁻²⁷

Building on the aforementioned collective observations, ADvance was designed as a double-blind placebo-controlled clinical trial to preliminarily assess the safety and efficacy of DBS-f for the treatment of very mild AD, as well as the utility of prespecified clinical and neuroimaging baseline

measures as predictors of response. While other targets along the Papez circuit could, at least in theory, be suitable or perhaps more optimal, we chose a target within the hypothalamus which contains both the descending portion of the fornix and the mammillary body. This was done based on our empirical observation of acute memory effects in a patient with hypothalamic stimulation for obesity²⁸ and the preliminary observations in the six AD patients in the pilot study of DBS for AD.¹⁵ Other potential targets would require validation of both safety and efficacy, something that was beyond the scope of our trial. Here, we describe the design and methods of the ADvance clinical trial and discuss the reliability of the major clinical outcome measures used in the study.

Methods

Overview

ADvance (ClinicalTrials.gov identifier: NCT01608061) is a feasibility clinical trial funded by the National Institute on Aging (R01AG042165) and Functional Neuromodulation Ltd (FNM). Six sites in the United States and one in Canada participated in enrollment (see “Acknowledgments” section). Sites were chosen based on previous experience with clinical research related to AD, neuroimaging capabilities, ethical approvals, and experience with DBS research.

ADvance is a 12-month double-blind, placebo-controlled, masked clinical trial, as shown in Figure 1. Consenting individuals participated in a screening visit followed by a baseline visit to assess eligibility and collect baseline cognitive and other clinical assessments, historical documents, laboratory values, and neuroimaging. DBS device implantation took place within 60 days of consent. Two weeks following implantation, participants were randomized into two groups, DBS “on” or DBS “off”, for a 12-month blinded period followed by a 12-month open-label extension during which all subjects will be programmed to DBS “on”. Additional long-term clinical follow-up for up to 48 months will be provided.

Participants: inclusion and exclusion criteria

Inclusion

- Informed consent signed by the subject, caregiver, and a surrogate
- Nonchildbearing/postmenopausal women, and men between 45 and 85 years of age
- Met criteria for probable AD according to the National Institute of Aging/Alzheimer’s Association criteria²⁹

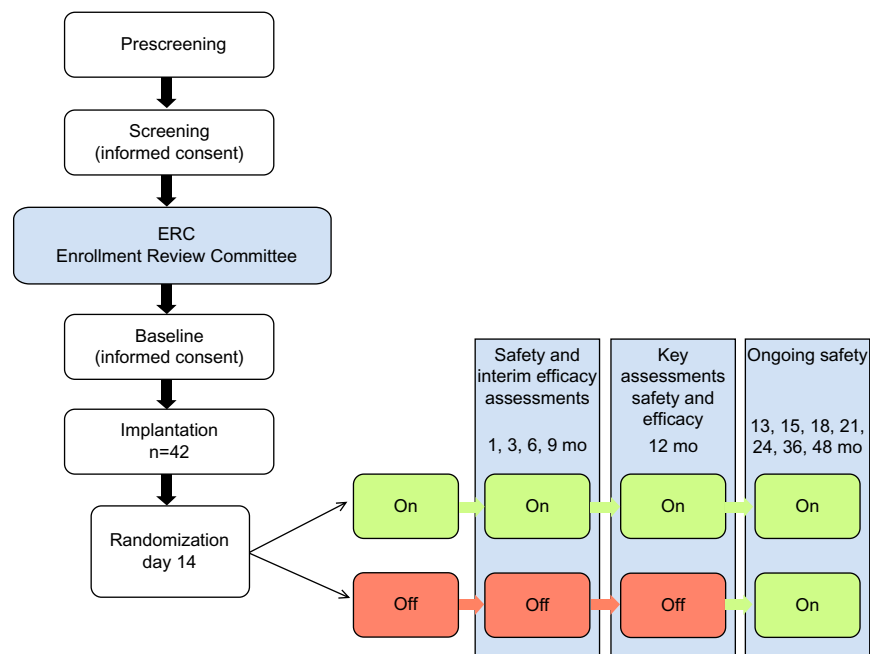


Figure 1 Flow diagram depicting an overview of the ADvance trial schedule. Major visits are shown along with the number of participants at implantation (n=42). Green indicates DBS “on”, red indicates DBS “off”.

Abbreviations: mo, months; DBS, deep brain stimulation.

- Clinical Dementia Rating scale (CDR global) rating of 0.5 or 1 at screening³⁰
- Alzheimer’s Disease Assessment Scale – cognitive component (ADAS-cog-11) score of 12–24, inclusive, with a score ≥ 4 on ADAS-cog item 1 (immediate recall) at both screening and baseline visits^{30,31}
- General medical health rating ≥ 3 (good or excellent)³²
- Living at home with an available caregiver or informant to report on daily activities and function throughout the study
- Fluent in English
- Good surgical candidate for placement of a deep brain stimulator, as determined by the neurosurgical team
- On a stable dose of a acetylcholinesterase inhibitor (AChEI) donepezil, galantamine, or rivastigmine for at least 60 days prior to signing informed consent, without intention to modify this medication dose throughout the entirety of the study.

Exclusions

- Neuropsychiatric Inventory (NPI)³³ total score ≥ 10 or score ≥ 4 in any domain except apathy at screening
- Modified Hachinski ischemic score > 4 at screening³⁴
- Young Mania Rating Scale (YMRS) ≥ 11 at screening³⁵
- Attempted suicide in the 2 years prior to signing consent
- Risk for suicide as determined by an answer of “yes” to “suicidal ideation” or “yes” to any items in the suicidal

behavior section with reference to the 3-month period prior to screening on the Columbia Suicide Severity Rating Scale (C-SSRS)³⁶

- Current major psychiatric disorder
- Score > 10 on the Cornell Scale for Depression and Dementia (CSDD) at screening³⁷
- History of head trauma in the 2 years prior to signing consent
- History of brain tumor, subdural hematoma, or other clinically significant space-occupying lesions on CT (computed tomography) or MRI (magnetic resonance imaging)
- Mental retardation
- Current alcohol or substance use disorder as defined by *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition – text revision (DSM-IV-TR)
- Exclusions for PET and MRI, including claustrophobia, metal implanted in the body (MRI), and insulin-dependent diabetes (PET)
- Radiation exposure in the year prior to consent that added to exposure in the study would exceed 5 rem over 12 months
- Any abnormal laboratory results, cardiovascular or neurovascular disorders, or currently prescribed non-AD medications that would preclude participation in the study
- Unstable doses of any medication prescribed for the treatment of memory loss or AD

- Unwilling or unable to comply with the protocol
- Life expectancy of <1 year
- Actively enrolled in another concurrent clinical trial.

Recruitment and consent

Participants were recruited from memory and geriatric psychiatry clinics, advertising, and community outreach activities at each of the seven sites. Prospective participants were first assessed for their ability to provide consent through clinical interviews. Clinicians experienced in dementia research and DBS surgery evaluated each participant's ability to comprehend the consent form as well as understand the personal consequences of what would and could happen during the study. Assessments and consent procedures took place in the presence of a caregiver who cosigned the consent form as a witness. Voluntary written informed consent by each subject and his or her caregiver was required at the beginning of both the screening and baseline visits and prior to surgical implant procedure (if all entry requirements were met).

Eligibility screening

Enrollment was defined as the time a subject signed the screening informed consent to participate and was followed by an initial screening visit at which medical and neuropsychiatric information was gathered (Table 1). In order to move forward with implantation, a site-independent Enrollment Review Committee (ERC) reviewed the data collected to determine if subjects met inclusion and exclusion criteria. For each subject, the ERC reviewed historical documentation of early AD as well as scores on cognitive tests conducted during the screening visit to confirm the diagnosis of probable AD. They also verified the absence of concomitant medical or psychiatric conditions or medications, and any surgical risks that might affect DBS surgery. Additionally, US trial sites audio-recorded selected psychometric assessments, and site-independent ERC raters dually scored a randomly selected sample of ADAS-cog and CDR interviews to confirm scoring accuracy and rater consistency.

Baseline visit and DBS device implantation

Baseline visit and surgery

A baseline visit was scheduled ≤ 59 days postconsent at which baseline medical, laboratory, neuropsychological, and imaging data (PET and MRI) were obtained (Table 1).

Implantation surgery took place within 60 days following screening consent if all study requirements were met.

High-resolution, stereotactic MRI scans of the brain were used to directly target the bilateral postcommissural fornices. More specifically, the DBS electrode was implanted 2 mm anterior and parallel to the vertical portion of the fornix within the hypothalamus (Figure 2). The most ventral contact of the DBS lead (Medtronic model 3387) was typically placed posteromedial to the optic tract at a depth such that the dorsal most contact was intraparenchymal, approximately at the level of the midcommissural plane. Laterally, the target corresponded to the midpoint of the medial/lateral extent of the fornix in the coronal plane to maximize the proximity of the four DBS contacts to the descending column of the fornix. A burr hole was placed approximately 2.5 cm lateral to the midline at or just anterior to the coronal suture with adjustments made so that the lead trajectory would avoid sulci and deflection from the wall of the frontal horn of the lateral ventricle. Intraoperative stimulation was performed at the discretion of the surgeon to evaluate contact position. After surgery and prior to hospital discharge, an MRI was conducted to confirm the position of the leads. If necessary, the implanting surgeon repositioned the leads during the same hospitalization, followed by a second MRI. A third-party-blinded determination of lead position was obtained by sending the postimplant MRI scan to a neurosurgeon not involved with surgical implantation of devices for the study, who subsequently performed stereotactic analysis of the MRI on a DBS planning station.

Surgical devices and programming

The DBS system used in the study includes the Model 37601 Activa® PC stimulator, Model 3387 Lead, and Model 37085 extension (Medtronic, Inc., Minneapolis, MS, USA). All implantable devices, external control devices, and accessories (Model 8840 N'Vision® programmer with 8870 Activa applications software and Model 37022 External neurostimulator) are approved by the FDA for DBS treatment of Parkinson's disease and essential tremor. The Activa PC neurostimulator (Medtronic, Inc.) is a dual-channel device capable of delivering bilateral stimulation. It contains a nonrechargeable battery and microelectronic circuitry that delivers controlled electrical pulses to specifically targeted brain areas. The device was implanted subcutaneously just inferior to the clavicle, connected to an extension run subcutaneously along the head, neck, and shoulder and connected to the implanted leads. Quadripolar DBS leads (3387) are made of four thin, insulated coiled wires bundled with polyurethane insulation. Each lead has four 1.5 mm

Table I ADvance visit schedule

	Screen	Baseline	Implant	Program	Months post-DBS device implant												
					1	3	6	9	12	13*	15*	18*	21*	24*	36*	48*	
Procedures																	
Consent	✓		✓														
Review of medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Medical history	✓																
Physical examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Electrocardiogram	✓																
Preoperative lab tests ^a	✓	✓															
Monitoring lab tests ^b	✓		✓		✓		✓		✓								
Imaging																	
PET		✓			✓		✓		✓								
MRI		✓	✓						✓								
Psychiatric consult	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CSDD	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
YMRS	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
C-SSRS	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Neuropsychological testing																	
ADAS-cog	✓	✓			✓	✓	✓	✓	✓			✓		✓	✓	✓	
CDR	✓	✓				✓	✓	✓	✓			✓		✓	✓	✓	
NPI	✓	✓				✓	✓	✓	✓			✓		✓	✓	✓	
CVLT		✓				✓	✓	✓	✓			✓		✓			
Digit span		✓				✓	✓	✓	✓			✓		✓			
Digit symbol		✓				✓	✓	✓	✓			✓		✓			
Letter fluency		✓				✓	✓	✓	✓			✓		✓			
Trail Making Test		✓				✓	✓	✓	✓			✓		✓			
BVMT-R		✓				✓	✓	✓	✓			✓		✓			
ADCS-ADL23		✓				✓	✓	✓	✓			✓		✓			
QOL-AD		✓				✓	✓	✓	✓			✓		✓			
ZBI		✓				✓	✓	✓	✓			✓		✓			
Hachinski ischemic scale	✓																
DBS device implantation			✓														
Randomization				✓													
Device program “on”/“off”				✓					✓								
Unblinding															✓		

Notes: *indicates all the devices programmed "on" for open-label follow-up. Phone follow-up will occur at months 27, 30, 33, 39, 42, 45 to assess adverse events or mood, memory, or personality changes. ^aCBC, INR, PT, PTT, complete metabolic profile; ^bTSH, free T₃, free T₄, prolactin, LH, FSH, free testosterone, ACTH, cortisol, glucose, complete metabolic profile.

Abbreviations: ACTH, adrenocorticotropic hormone; CBC, complete blood count; ADAS-cog, Alzheimer's Disease Assessment Scale – cognitive component; ADCS-ADL23, Alzheimer's Disease Cooperative Study – Activities of Daily Living; BVMT-R, Brief Visuospatial Memory Test – Revised; CDR, Clinical Dementia Rating Scale; CSDD, Cornell Scale for Depression and Dementia; C-SSRS, Columbia Suicide Severity Rating Scale; CVLT, California Verbal Learning Test; DBS, deep brain stimulation; FSH, follicle-stimulating hormone; INR, international normalized ratio; LH, luteinizing hormone; MRI, magnetic resonance imaging; NPI, Neuropsychiatric Inventory; PET, positron emission tomography; PPT, partial prothrombin time; PT, prothrombin time; QOL-AD, Quality of Life – Alzheimer Disease; TSH, thyroid-stimulating hormone; YMRS, Young Mania Rating Scale; T₃, free triiodothyronine; T₄, free thyroxine; ZBI, Zarit Burden Interview.

electrodes at the tip spaced 1.5 mm apart. Stimulation can be delivered using one electrode or a combination of electrodes. The N'Vision programmer (8840) is an external component that noninvasively reviews and adjusts the neurostimulator's output parameters.

Randomization, blinding, and DBS-f dosing

The overall study design was a delayed-start trial, in which all subjects received DBS stimulator implantation and were

randomly allocated to begin DBS-f soon after implantation or 1 year later. Patients were randomized 2 weeks after implantation in a 1:1 allocation to DBS-f "on" or DBS-f "off". Random blocks were used to generate randomization for each site, and the randomization assignment was provided via phone call to the unblinded technician responsible for programming the implanted device. Study subjects, the implanting surgeon, study coordinators, the principal investigator, and follow-up clinicians responsible for administering questionnaires and

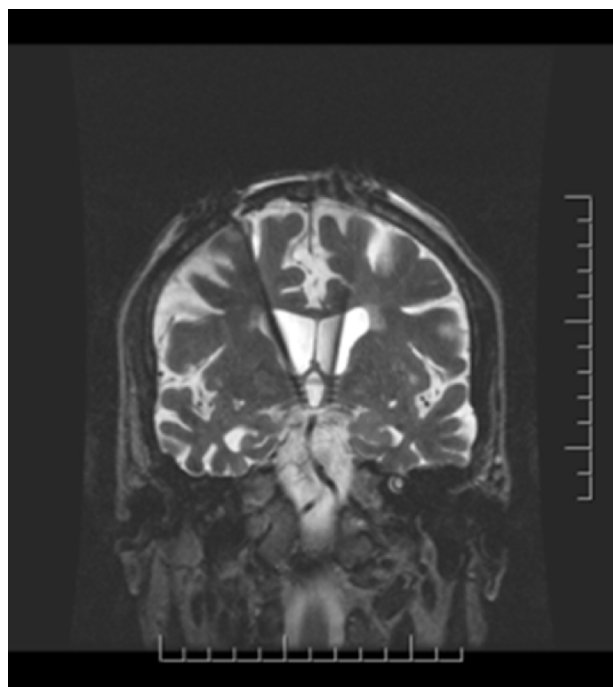


Figure 2 Coronal MRI demonstrating placement of the DBS electrodes anterior and parallel to the vertical portion of the fornix within the hypothalamus bilaterally.
Abbreviation: DBS, deep brain stimulation.

outcome assessments remain blinded to treatment assignment until all subjects complete the 12-month visit or until each subject's 24-month visit, whichever occurs first. Instances of emergency unblinding are disclosed to site monitors and the national primary investigators (CGL and AML). These procedures are only initiated in cases of compromised subject welfare and are, whenever possible, reviewed by the national and site primary investigators and reported to the commercial sponsor (FNM).

At a follow-up visit 11–17 days following surgery, the DBS device was programmed according to the randomization assignment by an unblinded clinician (Table 1). Starting with the most ventral contact, monopolar stimulation was delivered at a frequency of 130 Hz with a 90-microsecond pulse width. The initial amplitude was set to 1 V and was increased incrementally by 1 V every 30–60 seconds to a maximum until the subject reported experiential phenomena, including memory-related phenomena or autonomic symptoms (eg, increased heart rate). Each contact was individually tested, and the contact on each side that produced an experiential or autonomic-related event at the lowest voltage was chosen as the therapeutic contact. If no experiential phenomena were produced with stimulation, the contact that had the highest threshold for autonomic adverse effects was chosen. This was usually contact 2 or 3, the two most superior of the four contacts on the DBS electrodes. For each subject randomized

to the DBS-f “on” group, the chosen contact on each side was set to a voltage of 50% of that eliciting a stimulation-related event or of 3.5 V, whichever was lower. If a stimulation-related event was reported with bilateral stimulation, the voltage was turned down in 0.2 V increments on each lead until the event was no longer experienced. For each subject randomized to the DBS-f “off” group, all leads were set at 0 V. The programming protocol was completed in full regardless of DBS-f “on” or DBS-f “off” randomization status to prevent unblinding of participants, with the only difference being the final voltage of the DBS-f electrodes. The unblinded clinician at each site is responsible for ensuring that the parameters remain consistent throughout the 24-month follow-up unless there are stimulation-associated side effects or safety concerns. Following the end of the 24-month follow-up visit, programming will be left to the discretion of the site physician.

Follow-up during the double-blind period

Follow-up visits are scheduled for 1, 3, 6, 9, and 12 months after implantation. These visits include a physical examination, psychiatric consultation, neuropsychological testing, blood tests (6, 12 months), PET scans (1, 6, 12 months), and brain MRI (12 months). All subjects, including patients randomized to DBS-f “off”, have the implanted device programmed “on” after the 12-month visit for a subsequent open-label treatment phase. Open-label follow-up visits are scheduled for 13, 15, 18, 21, 24, 36, and 48 months after implantation. These visits consist of safety monitoring, clinical updates, physical examination, psychiatric consultation, and/or neuropsychological testing (18, 24 months). There will be additional phone follow-ups at months 27, 30, 33, 39, 42, and 45 to assess any adverse events (AEs) or changes in cognition or personality. Subjects will exit the study at the conclusion of their 48-month visit (Table 1).

PET and MRI

MRI and PET protocols were implemented based on the AD Neuroimaging Initiative (ADNI) protocols that have been used extensively to measure longitudinal changes in gray matter volumes (MRI) and cerebral glucose metabolism across different MRI and PET scanners and study sites.^{38,39} PET scans with the radiotracer [¹⁸F]-2-deoxy-2-fluoro-D-glucose ([¹⁸F]-FDG) to measure regional cerebral glucose metabolism are acquired preoperatively and at 1, 6, and 12 months. PET scans are performed on a PET/CT scanner at each site using a uniform protocol and postprocessing

methods designed to obtain comparable measurements of cerebral glucose metabolism across scanners/sites.⁴⁰ During radiotracer uptake, subjects are maintained in a quiet, dimly lit room, with eyes open and ears unoccluded. Thirty minutes after a 5 mCi $\pm 10\%$ radiotracer injection, patients are positioned in the scanner, and a 20-minute emission scan is obtained, followed by a transmission scan. The second, 10-minute frame of the emission scan (40 minutes after [¹⁸F]-FDG administration) is used for quantitative analysis. The MRI protocol was designed to detect focal pathology (eg, tumors or strokes) and for MRI-PET registration to define regions of interest. The MRI scans were performed prior to the first PET scan, 1–2 days postoperatively, and are repeated at 12 months. MRI scans are acquired on 1.5 T scanners at each site. The sequences were implemented from the ADNI protocols that were developed for each MRI scanner to obtain comparable quantitative measurements, including gray matter volumes.^{38,39} The MRI sequences include 3-plane localizer, volumetric sequence (magnetization-prepared rapid gradient-echo or spoiled gradient recalled echo), T₂ sequences for electrode localization (postoperative scan only), fast spin-echo inversion recovery (FSE-IR), DTI (when available), and resting-state functional MRI (when available).

Safety monitoring

An independent Clinical Events Committee (CEC) consisting of a multidisciplinary team of physicians from geriatrics, neurology, and neurosurgery who are not investigators in the study was created. The CEC conducts reviews of all AEs reported for study subjects. Each AE is adjudicated for its relatedness to the study, surgical procedure, implantable pulse generator, leads (electrodes), and programming. AEs are categorized as general medical, psychiatric, surgical, or programming in nature. In addition, adjudications are made regarding whether an event is a serious AE or an unanticipated adverse device effect. Psychiatric AEs are assessed at each follow-up visit using measures such as the C-SSRS,³⁶ CSDD,³⁷ and YMRS.³⁵

A separate independent Data Safety and Monitoring Board (DSMB) of one practicing neurosurgeon, two neurologists and/or psychiatrists, and one biostatistician not connected to the sponsor or participating investigators was established. The DSMB reviews CEC-adjudicated AEs, occurrences of serious AEs and unanticipated adverse device effects, as well as safety and efficacy trends and makes recommendations regarding the continuation, suspension, or termination of the study. Following each review by the

DSMB, a summary of results is sent to the FDA and filed with all overseeing institutional review boards.

Outcome measures and analytic plan

Safety outcome assessment

Doctors and clinical staff at local sites are in regular contact with participants and study partners to monitor for AEs, as described earlier. As soon as an AE is detected, the local team obtains as much clinical information as possible and rapidly reports to the study principal investigator, the medical monitor, and the coordinating center. The coordinating center, working as a team, then reviews, requests additional information, notifies other sites, and notifies DSMB, institutional review boards, and FDA as spelled out in study procedures. AEs will be presented as a measure of the safety of DBS-f surgery and treatment for mild AD.

Clinical outcome assessment

One primary goal of this study is to examine the acute and long-term safety of DBS-f for mild AD. Acute safety is assessed by the rate of serious device- or procedure-related AEs from the date of implant through the date of randomization as well as serious procedure-related events through 30 days postimplant. Long-term safety is assessed by the rate of serious therapy (programming) related AEs from the date of randomization through the date of the 12-month visit.

The second goal of this study is to preliminarily examine the efficacy of DBS-f for mild AD. The two primary outcomes are change from baseline in the ADAS-cog and CDR sum of boxes (CDR-SB) scores. The ADAS-cog is one of the more commonly used measures to assess cognitive symptoms associated with AD in clinical trials. The ADAS-cog is able to differentiate individuals with nonimpaired cognition from those with impaired cognition and has demonstrated reliability in assessing the extent of cognitive impairment in individuals.⁴¹ The standard ADAS-cog consists of 11 subscales designed to assess memory, language, and praxis, and scoring is based on the number of errors made on each item, with a higher score indicating greater impairment. Previous clinical trials have indicated that a four-point change on the ADAS-cog total score is suggestive of a clinically important difference.^{42,43} However, systematic analysis of double-blind placebo-controlled trials of cholinesterase inhibitors demonstrated an average -2.7 improvement at 6 months and 1 year.⁴⁴ The CDR was developed for the evaluation of staging severity of dementia.⁴⁵ The CDR characterizes cognitive and functional performance by assessing the subject in six domains including memory, orientation, and problem solving.

The CDR has consistently demonstrated good reliability^{46,47} and has been validated against neuropathological findings.^{48,49} A global CDR score is computed via an algorithm based on the input of the ratings of the six domains and is useful for characterizing and tracking a subject's level of impairment and stage of dementia severity,⁴⁵ with values between 0 (normal) and 3 (severe dementia). The CDR-SB score is obtained by summing each of the six domain ratings. CDR-SB scores range from 0 to 18, with higher scores reflecting more severe impairment.⁴⁶

Secondary outcomes include change from baseline to 12 months in scores on other cognitive tests: California Verbal Learning Test, second edition (CVLT-II⁵⁰); Verbal Fluency;⁵¹ Brief Visuospatial Memory Test – revised version;⁵² and Trail Making Test.⁵³ Other measures include Quality of Life – AD, which is a rating of the patient's quality of life both from the patient and the caregiver,⁵⁴ AD Cooperative Study – Activities of Daily Living Inventory, Zarit Burden Interview to assess caregiver distress,⁵⁵ and NPI to assess the presence of psychiatric symptoms and behaviors.³³

Neuroimaging outcome assessment

The primary neuroimaging outcome measure is a regional change in glucose metabolism from baseline to 12 months, measured by PET. Previous research using PET measures of cerebral glucose metabolism has identified a specific pattern in AD of hypometabolism in the parietal and temporal heteromodal association cortices.⁵⁶ This pattern has been found in over 85% of pathologically confirmed AD cases⁵⁶ and has been correlated with dementia severity.⁵⁶ FDG-PET is sensitive to AD clinical progression and to effects of pharmacotherapy, including DBS.^{15,26,57–59}

A secondary imaging outcome is bilateral hippocampal volume measured using volumetric methods, decreases in which have been correlated with the progression of AD.^{21,22} An additional imaging tool of interest is fornix integrity measured with DTI for which the fornix is manually drawn (with high reliability) as a region of interest. However, we do not plan to use DTI obtained after implantation analytically due to concerns about interference by the implanted electrodes.

Clinical measure analytic plan

All analyses will be conducted according to the prespecified statistical analysis plan for the study. Descriptive statistics compare treatment group on baseline demographics. Categorical variables are analyzed using frequency, incidence, and event rate. For continuous variables, analyses include mean, median, standard deviation, and range.

For the acute safety end point, rate and 95% confidence interval will be presented. For long-term safety end points, rate and 95% confidence interval will be compared according to randomization group. Other data summaries will include a detailed summary and rate estimation of all serious AEs, as well as Kaplan–Meier estimates of the cumulative rates over time.

For the two clinical efficacy outcomes of particular interest (ADAS-cog score and CDR score), all analyses will follow intent-to-treat (ITT) or modified-ITT principles. The mean change from baseline (preimplant) to 12 months postimplant will be calculated in each group. Differences between randomized groups in mean change on each of these primary outcomes will be calculated, along with corresponding two-sided 95% confidence intervals. In addition, within group improvements will be assessed relative to a null change of zero. Additional analyses will include assessments of change over time in mixed model regression estimations with repeated measurements. Site will be used as a covariate in this model.

In addition to ADAS-cog-13 total score, this method will also be used to examine derived Word Recall Total score, Word Recognition scores, and the subset of five ADAS-cog items shown to be most sensitive to memantine. The subsetting methodology described by Ihl et al⁶⁰ will be applied to this data set to assess the relative strength of treatment effect across other subtests of the ADAS-cog. Further analyses will be conducted to determine the impact of baseline ADAS-cog scores on outcome (ie, to assess whether the treatment effect diminishes in the more advanced population), including mixed model regression analyses with baseline ADAS-cog score as a predictor, and fit with an interaction term. Within-group outcomes, by baseline ADAS-cog score also will be summarized. CDR analyses will include global score, SB, and memory domain score. In addition we will analyze the CDR-SB score relative to the overall severity classification from the ADAS-cog to determine the agreement of categorization of mild symptom severity at baseline with how the scores change together over time.

Neuroimaging measure analytic plan

The end point is the mean, per-subject, percent glucose metabolism change in prespecified regions of interest, including the subdivisions of the temporal and parietal association cortex and the hippocampus. The primary analysis will be conducted on an ITT basis. The percent improvement for each subject will be determined by subtracting the baseline value for glucose metabolism in each region of interest (ROI-BL) from the

12-month glucose metabolism (ROI-12) and dividing the result by ROI-BL ($[\text{ROI-12} - \text{ROI-BL}]/\text{ROI-BL}$). This quantity will be averaged across all subjects, and mean improvement will be compared across randomization groups in a two-sample *t*-test evaluated at the 0.05 significance level. Supportive analyses will only evaluate those subjects with complete data and/or those who are compliant with the protocol.

Exploratory analyses will be conducted to evaluate the relationship between changes in regional glucose metabolism and changes in clinical outcomes (eg, ADAS-cog, CVLT, etc). Exploratory analyses will be performed to identify baseline structural and functional neuroimaging predictors of DBS clinical response. These analyses may include, but not be limited to, regional glucose metabolism, hippocampal volumes, and regional white matter functional integrity (DTI). These analyses will fit multivariate linear regression models, with the candidate predictor and randomization assignment, and their interaction as independent variables, and clinical outcome (eg, ADAS-cog-11, CDR-SB, CVLT) as the dependent variable. Covariates with apparent effect on outcome will then be fit in a multivariate regression model with stepwise selection procedure using significance level of 0.10 as a cutoff.

Power estimation

The power to detect a treatment effect depends on the size of the effect, sample size, and the configuration of the within-person variance–covariance matrix. For the ADAS-cog, we conducted a power simulation using ADNI data. Assuming a mixed effects model with random intercept and slope, no missing data, variance of intercept $= (4.68)^2$, variance of slope $= (0.37)^2$, correlation between random intercept and random slope of 0 (model with unstructured covariance failed to converge), variance of residuals $= (5.87)^2$, time vector = c(0,3,6,9,12), there is 84% power to detect a difference in change scores of 7.53 points with 42 subjects, which translates to a difference in slopes of 0.63. We will have 80% power to detect a difference in slope of 0.588 points/month or 7.06 points/year. Using the same method, the power to detect a difference in a change of score of 4.0 points (a typical effect size) was calculated to be 36%, which translates to a difference in slopes of 0.33.

Statistical power for the neuroimaging hypothesis listed previously was estimated using PASS 2008 software under a two-sided, two-sample *t*-test and the assumption of 40 randomized subjects in a 1:1 allocation. Assuming a significance level (α) of 5%, mean improvement (DBS) of 10%, standard deviation (DBS and control) of 12%, and mean improvement (control) of 0.0%, a total of 40 randomized subjects provides

at least 80% power to statistically evaluate the end point of glucose metabolism as specified earlier.

Results

Characterization of the baseline study population

Following recruitment, 85 potential subjects across the seven study sites signed the initial consent and participated in a screening visit. Forty-eight (56.5%) met all inclusion and exclusion criteria at screening and were approved by ERC reviewers to proceed in the trial. Forty-two of these 48 patients (49.4% of consenting potential subjects) met all criteria following the baseline visit, signed a second consent form, and underwent DBS-f device implantation. The six patients who were cleared at screening but did not proceed to implant did so for two reasons: two declined to proceed and did not sign consent for baseline testing, and four failed to meet inclusion/exclusion criteria when ADAS-cog was repeated at baseline, with scores out of range.

We compared (Table 2) consenting subjects who were screened and successfully implanted ($N=42$) to those who were screened but not implanted with a DBS device ($N=43$). We saw no difference between these groups in demographic information (age, sex, and elapsed time since initial AD diagnosis) gathered at screening. We observed significantly lower (ie, better) ADAS-cog-11 (17.5 ± 3.6 vs 21.1 ± 9.8 , $P=0.03$) and CDR global scores (67% vs 38%, with a score of 0.5, $P=0.05$) in subjects who were implanted. This is explained by the inclusion and exclusion criteria designed to limit participation to subjects with very mild AD. Approximately 40% of patients who failed screening did so because symptom severity was too high. No significant difference was found in CDR-SB score, Hachinski ischemic scale score, or psychiatric assessment measures, including the NPI, C-SSRS, CSDD, or the YMRS in implanted compared to not implanted patients (Table 2).

Table 2 summarizes the scores of implanted subjects on additional cognitive and psychiatric tests from the baseline visit. In addition to inclusion criteria measures such as the CDR, scores on the CVLT-II, a verbal memory measure, were similar to published scores of individuals with MCI who later progressed to AD.⁶¹ Note that these additional scores include all 48 subjects who were assessed at baseline, not only the 42 who were implanted.

Reliability of primary outcome measures

We examined test–retest reliability of the main outcome measures by comparing score stability between the screening and baseline visits for the 42 implanted subjects. There was

Table 2 Demographics and screening measures by implantation status

Patient characteristic	Screened and implanted (n=42)	Screened and not implanted (n=43)	P-value*
Age (years)	68.2±7.8	66.8±7.4	0.41
Sex (male)	55%	47%	0.45
Elapsed time since initial diagnosis of AD (years)	2.5±1.9	1.6±1.4	0.06
ADAS-cog-11 score	17.5±3.6	21.1±9.8	0.03
ADAS-cog-13 score	28.9±5.2	32.3±11.4	0.08
CDR global score: 0.5	67%	38%	0.05
CDR global score: 1	33%	57%	
CDR global score: 2		5%	
CDR sum of boxes score	3.9±1.6	4.5±2.3	0.30
NPI total score	2.8±2.8	4.7±7.1	0.12
Hachinski ischemic scale score	0.5±0.6	0.4±0.5	0.34
C-SSRS score	0.2±0.8	0.3±0.7	0.74
CSDD score	1.8±2.1	2.2±3.6	0.54
YMRS score	0.18±0.58	0.16±0.50	0.89
GMHR score ^a	3.9±0.3	NA	
CVLT-II – sum of first five recall trials A ^a	20.3±9.1	NA	
CVLT-II – short delay free recall A ^a	1.9±1.9	NA	
CVLT-II – short delay free recall C ^a	3.6±2.5	NA	
CVLT-II – long delay free recall A ^a	1.5±2.2	NA	
ADCS-ADL23 score ^a	69.5±6.0	NA	

Notes: *P-values for continuous measure calculated by t-tests; P-values for discrete measures calculated by chi-squared tests; ^adata gathered at baseline visit.

Abbreviations: AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale – cognitive component; ADCS-ADL23, Alzheimer's Disease Cooperative Study – Activities of Daily Living; CDR, Clinical Dementia Rating Scale; NPI, Neuropsychiatric Inventory; CSDD, Cornell Scale for Depression and Dementia; C-SSRS, Columbia Suicide Severity Rating Scale; CVLT-II, California Verbal Learning Test, second edition; GMHR, General Medical Health Rating score; NA, not applicable; YMRS, Young Mania Rating Scale.

a moderate correlation between screening and baseline visit scores for ADAS-cog-11 and a high correlation for ADAS-cog-13, CDR global score, CDR-SB, and NPI (Table 3). The stability in scores seen within subjects across initial visits suggests that our primary clinical outcome measures are reliable for the population in this study and can be used to measure disease progression over time in this trial.

Discussion

ADvance is the first multicenter, randomized, double-blind controlled clinical trial evaluating the efficacy of DBS-f for mild AD. This paper outlines the methods used in the ADvance trial and characterizes the study population. Subjects demonstrate cognitive test scores indicative of mild

Table 3 Correlation* between screening and baseline value

Measure	N	Pearson's correlation	Intraclass correlation	Kappa
ADAS-cog-11 score	42	0.42	0.41	
ADAS-cog-13 score	42	0.54	0.51	
CDR global score	42			0.68
CDR sum of boxes score	42	0.68	0.69	
NPI total score	42	0.59	0.60	

Notes: *The kappa statistic is reported for the CDR global score; the Pearson and intraclass correlation coefficients are reported for all the other measures.

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale – cognitive component; CDR, Clinical Dementia Rating scale; NPI, Neuropsychiatric Inventory.

AD, and implanted participants differ from consenting non-implanted participants only on average ADAS-cog-11 and CDR global scores. Furthermore, we confirm the reliability of the primary outcome measures used in the ADvance study population by demonstrating consistency across two visits.

ADvance joins three smaller DBS studies conducted in AD patients published thus far⁶² and builds on data from approximately 25 animal studies.^{23,24,28,63} ADvance was designed based on an open-label Phase I study of DBS-f conducted in six patients with mild AD, as previously discussed. Interestingly, patients with less severe prestimulation cognitive dysfunction and less severe metabolic deficits were more likely to benefit from DBS-f in this trial.¹⁵ This study provided the basis for the inclusion criteria used in ADvance, which focus on selection of participants with very mild AD. Implanted participants were younger, more likely to be male, and had lower baseline ADAS-cog-11 scores than the mean scores in recently reported Phase III trials of amyloid-lowering agents in AD.^{64–66} Mean ADAS-cog-11 was 17.5 for implanted ADvance participants, and ranged from 19 to 23 in recent Phase III trials. Thus, our participants were younger and less impaired than those in these Phase III trials, but the differences were relatively small.

Fontaine et al⁶⁷ recruited 110 patients with Alzheimer dementia or MCI to be screened for a study assessing DBS for cognitive decline, and one subject met criteria, consented, and continued on to implantation. In the current study, 42 of 85 screened subjects consented and underwent implantation. One possible explanation for this difference may be that the Fontaine et al⁶⁷ study required subjects to have received a *DSM-IV* AD diagnosis within 2 years and have a mini-mental state examination score between 20 and 24, which was not required in the ADvance study. It also is possible that the 1-year open-label follow-up phase used in ADvance may have contributed to improved participation.

Another study in 2014 examined open-label DBS targeting the nucleus basalis of Meynert in six patients meeting criteria for mild-to-moderate AD. Although ADAS-cog scores worsened by an average of 3 points after 1 year of stimulation, the authors noted that this was less than the average 6- to 7-point worsening seen in prior reports of patients with AD. Further, global increases in metabolism in amygdalohippocampal and temporal regions were seen in three out of the four patients who underwent PET scans of cerebral glucose metabolism.⁶⁸

Taken in the context of prior research, ADvance is a novel, important step in studying DBS-f as a treatment for mild AD. The subject pool is much larger than prior studies and involves 1 year of double-blind, controlled cognitive testing and neuroimaging. The 1-year duration of the controlled comparison increases the likelihood of identifying significant differences between the stimulated (treatment arm) and non-stimulated (control arm) cohorts in this slowly progressive disorder. The 1-year blinded, controlled phase of the study is followed by up to 3 years of continued open-label follow-up with all patients being stimulated, which affords systematic pre- and postassessment of outcomes in about half the participants, and 2 years of additional follow-up. While the primary objective of the study is to evaluate safety, the larger subject population and controlled design affords preliminary testing of the efficacy of DBS-f in delaying cognitive decline and improving cortical glucose metabolism.

The ADvance methodology outlined here is strengthened by recruitment from seven sites with experienced investigators and rigorous subject selection by an independent ERC. The primary clinical outcome measures are standardized and validated and have been widely used so that the results of the current study can be evaluated in comparison to studies that tested other symptomatic treatments such as cholinesterase inhibitors.⁶⁹ The neuroimaging outcome measures, especially cerebral glucose metabolism, have also been well studied in AD^{56,57,70,71} and enable us to examine changes in brain function throughout the trial. Limitations of ADvance include limited sample size. Although larger than prior DBS studies, there are only 21 patients in each of the masked treatment groups. The goal is that the results of ADvance will inform a larger-scale clinical trial focused primarily on efficacy, rather than on safety, of DBS-f as a treatment for mild AD.

Research elucidating the neurobiological mechanism of DBS treatment for neurodegenerative diseases such as AD remains limited. While we hypothesize that this treatment works by stimulation of fornix-hippocampal-cortical circuits, and potentially even promotes neurogenesis in the hippocampus, this remains unproven. The memory circuits

we are examining may be undergoing degeneration at varying rates in individual study participants, limiting the effectiveness of DBS-f to slow cognitive decline and our ability to examine the efficacy of DBS-f within our study population.

In summary, the ADvance trial was successful in enrolling appropriate patients for a novel application of DBS, and we believe several unique design aspects outlined here could be considered in future clinical trials of DBS targeting AD and other cognitive disorders.

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Chair's office at Johns Hopkins University and University of Toronto: Constantine G Lyketsos, MD, MHS, coprincipal investigator; Elizabeth Plank Althouse, professor and chair of psychiatry at Johns Hopkins Bayview; Andres M Lozano, MD, PhD, FRCSC, FACS, co-principal investigator, professor, and Chair of Neurosurgery, Tasker Chair of Functional Neurosurgery; Gwenn Smith, PhD, imaging core director, professor of psychiatry and behavioral sciences, Johns Hopkins University; Cynthia Munro, PhD, neuropsychologist, associate professor of psychiatry and behavioral sciences, Johns Hopkins University; Esther Oh, MD, medical monitor, assistant professor of geriatric medicine, Johns Hopkins University; Jeannie Sheppard Leoutsakos, PhD, data core leader, assistant professor of psychiatry and behavioral sciences, Johns Hopkins University.

Clinical trial sites

Johns Hopkins University School of Medicine, Baltimore, MD: Paul Rosenberg, MD, associate professor, associate director, Memory and Alzheimer's Treatment Center; William S Anderson, MD, associate professor of neurosurgery.

University of Toronto/Toronto Western Hospital: Andres M Lozano, MD, PhD, FRCSC, FACS, professor of neurosurgery, Tasker Chair of Functional Neurosurgery; David F Tang-Wai, MDCM FRCPC, associate professor of neurology.

Banner Alzheimer's Institute, Phoenix: Anna Burke, MD, geriatric psychiatrist, dementia specialist; Francisco A Ponce,

MD, associate professor of neurosurgery, director of Barrow Center for Neuromodulation.

Banner Sun Health Research Institute, Sun City: Marwan Sabbagh, MD, director, Banner Sun Health Research Institute; Francisco A Ponce, MD, associate professor of neurosurgery, director of Barrow Center for Neuromodulation.

Brown University, Rhode Island Hospital, Butler Hospital: Stephen Salloway, MD/MS, professor of neurology, director of neurology and memory and aging program; Rees Cosgrove, MD/PhD, chair of neurosurgery; Wael Asaad, MD/PhD, assistant professor of neurosurgery.

University of Florida – Gainesville: Michael S Okun, MD, professor of neurology, codirector of the Center for Movement Disorders and Neurorestoration; Kelly D Foote, MD, professor of neurosurgery, codirector of the Center for Movement Disorders and Neurorestoration.

University of Pennsylvania: David A Wolk, MD, associate professor of neurology, assistant director of Penn Memory Center; Gordon Baltuch, MD/PhD, professor of neurosurgery, director of the Center for Functional and Neurorestorative Neurosurgery.

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